REMARKS

Claims 7-45 remain pending in the instant application. Claims 7-12 have been withdrawn. Claims 13, 15, 17, 20, and 34 have been amended and claim 14 has been canceled. Accordingly, upon entry of this paper, claims 7-13 and 15-45 will remain pending in the instant application.

Support for the amendment to the claims may be found throughout the specification, including the originally filed claims.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants note the Examiner's indication that the Office Action mailed on June 4, 2002 has been withdrawn, and the restriction requirement mailed November 26, 2002 has been withdrawn and the species election has been maintained.

The Examiner also states that Applicants elected the species of '2a site, IL-4 ε promoter and Renilla mulleri GFP' in the Response filed on September 26, 2003. Applicants reiterate herein that the 2a site and the CD9 site, both of which can be additional components of the expression vector, are not related as species. CD9 is a diptheria receptor (HBEGF) accessory protein. The 2a site and the IRES site, in contrast, are both species of sites which allows for separation of the two selection genes. Accordingly, Applicants submit that the election of a species between a 2a site and a CD9 site is improper. In addition, Applicants reiterate that the term "selection gene" as defined in the specification means a reporter gene that by its presence in a cell (i.e., upon expression) can allow the cell to be distinguished from a cell that does not

contain the reporter gene. Therefore, HBEGF, GFP, drug resistance genes, and additional selection genes are all selection genes.

It is Applicants' understanding that the search will be extended to the remaining species upon a finding of allowability.

Priority

The Examiner has stated that "an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5))."

The instant application has been amended to include reference to the priority application in the first paragraph.

Drawings

The Examiner has indicated that "the drawings filed on 11/13/00 have been objected [to]. Applicants are requested to see the PTO 948 attached to the previous office action mailed on 6/4/02."

Applicants are in the process of preparing formal drawings, and will submit the formal drawings prior to issuance of the instant application.

Specification

The Examiner has stated that "the attempt to incorporate subject matter into this application by reference to several publications (non-patent literature) and provisional applications is improper because the various publications (e.g., page 15, [which] refers to [a] provisional application) refer to subject matter which is essential to practice the claimed

invention. The provisional application in page 15 is referring to several different GFPs used in the claimed method."

Applicants respectfully submit that the disclosure of the instant application was complete as of the filing date (see below). Moreover, that which is known in the art need not be included in the specification, and is, therefore, not essential to practice the invention (M.P.E.P. §2163(I)(A)). Furthermore, as stated in the M.P.E.P. §608.01(p)(I)(A), material contained within a pending U.S. application may be incorporated by reference. Therefore, Applicants respectfully submit that the incorporation by reference of the above-mentioned provisional applications is proper.

Rejection of Claims 34, 35, 36, and 45 Under 35 U.S.C. §112

The Examiner has rejected claims 34, 35, 36, and 45 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "this is a new matter rejection." In particular, the Examiner is of the opinion that

> [t]he limitations 'Renilla mulleri GFP', 'Ptilosarcus gurneyi GFP', and 'Aequorea GFP' claimed in Claims 34-36, 45 have [*sic*] no clear support in the specification and the claims as originally filed. The specification has not disclosed the different types of GFP or the source of GFP. The subject matter claimed in claims 34-36 and 45 broadens the scope of the invention as originally disclosed in the specification.

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that clear support for the terms "*Renilla mulleri*", "*Ptilosarcus gurneyi*", and "*Aequorea*" may be found in originally filed claim 2. Claim 2, as filed, specifically states that GFP may be selected from the group consisting of *Renilla mulleri*, *Ptilosarcus gurneyi*, and *Aequorea*. Furthermore, Applicants' specification, at for example, page 15, lines 21-22 lists *Renilla mulleri*, *Ptilosarcus gurneyi*, and *Aequorea* as examples of sources for GFP. Moreover, U.S. Application Serial No. 09/710,058, which is incorporated into the instant application by

reference (see page 15, line 23), contains the sequences for at least *Renilla mulleri* and *Ptilosarcus gurneyi*. The sequence of *Aequorea* was well known in the art and publicly available at the time the application was filed. Therefore, claims 34, 35, 36, and 45 comply with the written description requirement and Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 18, 23, 32, 34-36, and 45 Under 35 U.S.C. §112

The Examiner has rejected claims 18, 23, 32, and 34-36, 45 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner is of the opinion that

> [t]he specification has not disclosed the combination of the expression vectors as claimed in the instant claims. The specification has not shown in possession of the claimed expression vectors. Additionally, the specification disclosure of the use of different selectable genes and disclosure of CD9 is simply not adequate support to show possession of the claimed expression vectors. The specification has not shown the combination of different selectable marker genes (GFP, HBEGF, CD9, and drug resistance gene marker combination). And further the specification has not shown different GFP species obtained from Renilla mulleri, Ptilosarcus gurneyi, and Aequorea.

Applicants respectfully traverse the foregoing rejection and submit that Applicants had possession of the claimed invention at the time the instant application was filed. Applicants respectfully submit that Applicants' specification contains sufficient written description of each of the claimed vectors. As set forth above, the instant specification contains clear support for an expression vector wherein GFP is "*Renilla mulleri*", "*Ptilosarcus gurneyi*", or "*Aequorea.*" Accordingly, claims 34, 35, 36, and 45 are adequately described by Applicants' specification.

With respect to claim 18, CD9, and its inclusion in the vectors of the invention, is described in Applicants' specification at, for example, page 15, lines 20 -30, which states:

> [i]n a preferred embodiment, these constructs comprising the ***HBEGF gene can be fused as outlined herein to any number of detectable or selectable genes*** as outlined herein for other constructs, including green fluorescent protein (GFP) and all its derivatives (including those from Aquorea, Renilla and Ptilosarcus; see U.S.S.N. 60/164,592, filed 11/10/99 and its continuation-in-part application filed 11/10/00 (no serial number received yet), both of which are expressly incorporated by reference). ***For example, CD9 has been classified as a diphtheria receptor accessory protein, and can increase the sensitivity to diphtheria toxin up to 25 fold.*** CD9 is tightly associated with HBEGF on the cell surface, and it is a 27 kD cell surface protein with four transmembrane domains. It is generally expressed in pre-B cells, vascular smooth muscle, cardiac muscle and the distal tubules of kidney. ***Thus, CD9 fusions are included within the scope of the invention.*** Several suitable constructs are shown in the figures. ***(Emphasis added).***

Furthermore, Figure 18A illustrates an example of a vector as set forth in claim 18, which includes a nucleic acid encoding HBEGF, GFP, IRES, a 2a site, and a CD9 site. Therefore, one of ordinary skill in the art would clearly be able to recognize that Applicants were in possession of the claimed invention.

Claim 23 is directed to an expression vector comprising a first and second selection gene, wherein the first and second selection gene are fused such that transcription from a promoter operably linked to the first selection gene results in a single transcript encoding the first and second selection genes and further comprising an IRES site interposed between the first and second selection genes which allows for functional separation of the two selection genes, wherein either the first or second selection gene is an HBEGF gene, ***further comprising a CD9 site.***

Applicants respectfully submit that, as set forth above a CD9 site is clearly described in Applicants' specification. Furthermore, an example of a vector as set forth in claim 23 is set

forth in Figure 18B. Therefore, one of ordinary skill in the art would clearly be able to recognize that Applicants were in possession of the vector claimed in claim 23.

With respect to claim 32, Applicants respectfully submit that the specification provides support for the vectors of the invention comprising an additional selection gene selected which is a drug resistance gene selected from the group consisting of puromycin, neomycin, blastocidin, bleomyhcin, and hygromycin. For example, the specification, at page 13, lines 6-11, states:

> [i]n a preferred embodiment, ***additional reporter genes are used, particularly when inducible death genes are used. In a preferred embodiment, the additional reporter gene is a selection gene.*** The cells containing the death gene and the drug selectable gene are grown; if the appropriate drug is added to the culture, only those cells containing the resistance gene (and hence the death gene) survive. This ensures that the cells are expressing the death gene to decrease "false positives", i.e. cells that do not die because they do not contain the death gene. ***(Emphasis added).***

Furthermore, Applicants specification states that

> [s]election genes allow the selection of transformed host cells containing the vector, and particularly in the case of mammalian cells, ensures the stability of the vector, since cells which do not contain the vector will generally die. ***Selection genes are well known in the art and will vary with the host cell used. Suitable selection genes include, but are not limited to, neomycin, blastocidin, bleomycin, puromycin, hygromycin, and other drug resistance genes,*** as well as genes required for growth on certain media, including, but not limited to, His and Lev or His and Trp. In some cases, for example when using retroviral vectors, the requirement for selection genes is lessened due to the high transformation efficiencies which can be achieved. Accordingly, selection genes need not be used in retroviral constructs, although they can be. In addition, when retroviral vectors are used, the test vectors may also contain detectable genes as are described herein rather than selection genes; it may be desirable to verify that the vector is present in the cell, but not require selective pressure for maintenance. (see page 34, lines 11-22). ***(Emphasis added).***

Based on the above, Applicants' specification clearly describes the vectors of the invention, including the selection genes which are drug resistance genes, as set forth in claim 32. Thus, the instant specification satisfies the written description requirement for the claimed

invention and Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Claim Objections

Claim 34 is objected to because of the following informalities: claim 34 recites 'Renill Mulleri' which is supposed to be "Renilla mulleri'.

Claim 34 has been amended to correct the typographical error in the term "Renilla mulleri". Accordingly, Applicants request withdrawal of the objection to claim 34.

Rejection of Claim 28 Under 35 U.S.C. §102(e)

The Examiner has rejected claim 28 under 35 U.S.C. §102(e) as being anticipated by US Patent 6,613,563 Bl (Sosnowski *et al*). In particular, the Examiner is of the opinion that

> [t]he reference teaches adenovirus vectors comprising a targeting ligand. The reference teaches that the targeting ligand can be heparin binding growth factors, and heparin binding EGF like factor (HBEGF) (refers to the nucleic acid encoding HBEGF of the instant claims) (e.g., see column 11, column 22). The reference teaches heparin-binding epidermal growth factors (HBEGF) and DNA encoding HBEGF (e.g., see column 28). The reference teaches that the DNA sequence of the ligand is generally introduced into a plasmid in operative linkage with an appropriate promoter (refers to the promoter of interest of the instant claims) (e.g., see column 46). The reference teaches that in addition to the promoter internal ribosome binding site (IRES of the instant claims) (e.g., see column 49).

Applicants respectfully traverse the foregoing rejection. For a prior art reference to anticipate a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient* 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 28 is directed to an expression vector comprising from 5' to 3' a nucleic acid encoding HBEGF; an IRES site; and a promoter of interest.

U.S. Patent No. 6,613,563 describes gene therapy vectors. The vectors are viral constructs which have their native tropism modified or ablated. In one embodiment, the tropism of a virus is modified by using a ligand to re-target the vector. Examples of ligands include FGF proteins and HBEGF.

While U.S. Patent No. 6,613,563 mentions the use of a vector including an IRES site and a DNA sequence linked to a promoter, the reference does not describe the three components of the vector of claim 28 in the same orientation as set forth in claim 28. U.S. Patent No. 6,613,563 does not disclose an expression vector comprising HBEGF, an IRES site, and a promoter of interest, in order from 5' to 3'. U.S. Patent No. 6,613,563 discloses that a DNA sequence of interest is introduced into a plasmid in operative linkage with a promoter for expression (see column 46, lines 16-18). An IRES site is disclosed as an element which can increase the expression of the desired product. However, the orientation of the IRES site, the promoter, and the DNA of interest are not described. Therefore, U.S. Patent No. 6,613,563 does not teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 13-32 and 37-44 Under 35 U.S.C. §102(e)

The Examiner has rejected claims 13-32 and 37-44 under 35 U.S.C. §102(e) as being anticipated by US Patent 6,465,253 Bl (Wickham *et al*). In particular, the Examiner is of the opinion that

> Wickham et al teach vectors and methods for gene transfer to cells. The reference teaches modified adeno virus vectors comprising non-native amino acid sequences. The reference teaches non-native amino acid sequence of UTV or Universal Transfer Vector sequences. The reference preferably teaches the non-native amino acid sequence or UTV sequence comprises heparin binding motifs, and a stretch of 21 amino acids of the heparin binding epidermal

> growth factor like growth factor (HB-EGF) (refers to the HBEGF of the instant claims). The reference teaches adenoviral vectors, which can comprise additional sequences, a protease recognition sequence (refers to 2a site of the instant claims) (e.g., see column 17). The reference teaches that the vectors comprise additional marker genes such as gene encoding GFP (refers to the second selection gene or GFP of the instant claims) (e.g., see column 19). The reference teaches that the non-coding sequences include promoter sequences.

Applicants respectfully traverse the foregoing rejection. For a prior art reference to anticipate a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient* 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 13 is directed to an expression vector comprising a nucleic acid encoding HBEGF and a nucleic acid encoding a Green Fluorescent Protein (GFP), further comprising an internal ribosome entry site (IRES).

Claim 21 is directed to an expression vector comprising a first and second selection gene, wherein the first and second selection gene are fused such that transcription from a promoter operably linked to the first selection gene results in a single transcript encoding the first and second selection genes and further comprising an IRES site interposed between the first and second selection genes which allows for functional separation of the two selection genes, wherein either the first or second selection gene is an HBEGF gene.

Claim 25 is directed to an expression vector comprising, from 5' to 3', a nucleic acid encoding HBEGF; a 2a site; a nucleic acid encoding GFP; an IRES site; and a promoter of interest.

Claim 28 is directed to an expression vector comprising, from 5' to 3', a nucleic acid encoding HBEGF; an IRES site; and a promoter of interest.

Claim 38 is directed to an expression vector comprising a first and a second selection gene, wherein the first and second selection gene are fused such that transcription from a

promoter operably linked to the first selection gene results in a single transcript encoding the first and second selection genes and further comprising a site which allows for functional separation of the two selection genes, wherein the first selection gene is an HBEGF gene.

U.S. Patent No. 6,465,253 teaches vectors comprising a nucleic acid molecule encoding a chimeric protein comprising a "nonnative amino acid sequence," (a UTV sequence) which allows the protein to "bind and enter cells more efficiently." An example of a UTV sequence is a 21 amino acid portion of HBEGF.

The present invention is directed in part to expression vectors which may be used to screen candidate bioactive agents for modulators of the activity of, for example, an IL-4 inducible ε promoter, using, for example, the HBEGF/diphtheria reporting system. In particular, pending claims 13, 21, 25, and 28 are directed to expression vectors which comprise, at least, an IRES sequence and a nucleic acid encoding HBEGF. As set forth in Applicants' specification, the IRES site allows the translation of two different genes on a single transcript. U.S. Patent No. 6,465,253 fails to teach or suggest the use of an IRES sequence in the vectors described therein which encode UTV sequences. Furthermore, claim 37 is directed to expression vectors of the invention wherein the expression vectors are retroviral vectors. U.S. Patent No. 6,465,253 fails to teach or suggest retroviral vectors comprising an IRES sequence and a nucleic acid encoding HBEGF. Therefore, based on the foregoing, U.S. Patent No. 6,465,253 fails to teach or suggest each and every limitation of the claimed invention.

Claim 38 is directed to an expression vector comprising two selection genes, wherein the first selection gene is an HBEGF gene. The selection genes are fused such that transcription from a promoter operably linked to the first selection gene results in a single transcript encoding the first and second selection genes. Furthermore, the expression vector comprises a site which allows for functional separation of the two selection genes. Although U.S. Patent No. 6,465,253

describes the use of a vector comprising an HBEGF gene, the reference does not teach or suggest an expression vector comprising an HBEGF gene which is ***fused*** to a second selection gene or a vector comprising a site which allows for ***functional separation*** of the two genes.

Therefore, U.S. Patent No. 6,465,253 fails to teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 13-33 and 37-44 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 13-33 and 37-44 under 35 U.S.C. 103(a) as being unpatentable over publication No. US 2002/0168649 Al (Ferrick *et al.*) and U.S. Patent 6,465,253 (Wickham, *et al.*). In particular, the Examiner is of the opinion that

> [t]he claimed invention differs from the prior art teachings by reciting expression vectors comprising IL-4 ε promoter. Wickham et al teach modified vectors comprising non coding sequences comprising HBEGF sequence, GFP, additional marker genes and promoter sequences. Wickham et al do not teach IL-4 ε promoter. Ferrick et al teach candidate bioactive agents comprising a fusion nucleic acid. The fusion nucleic acid comprises an IL-4 inducible ε promoter (refers to the promoter of the instant claims) (e.g., see page 3, left column) and at least one reporter gene. The reference teaches that the reporter gene includes green fluorescent protein (GFP) (a second reporter gene or GFP of the instant claims) (e.g., see page 3, right column). The reference teaches that the IL-4 ε promoter is hooked to a second reporter gene, a death gene that may be epidermal growth factor receptor (e.g., see left column in page 4). The reference teaches that the death gene is hooked to the GFP using either [an] IRES site or protease cleavage site (refers to IRES site and 2a site) (e.g., see right column in page 4). The reference teaches that in addition to promoter of interest, such as IL-4 ε promoter and reporter gene, the fusion nucleic acids comprises additional components including other reporter genes (refers to the additional selection genes of the instant claims), protein cleavage sites, IRES sites (e.g., see page 6, right column). The reference teaches that the exogenous constructs, which may [be] in the form of an expression vector are retroviral vectors. The reference in figures 5B and 5C depict the disclosed constructs.

Applicants respectfully traverse the foregoing rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations*** (M.P.E.P. 2143).

U.S. Patent No. 6,465,253 teaches vectors comprising a nucleic acid molecule encoding a chimeric protein comprising a "nonnative amino acid sequence," (a UTV sequence) which allows the protein to bind and enter cells more efficiently. An example of a UTV sequence is a 21 amino acid portion of HBEGF.

As set forth above, U.S. Patent No. 6,465,253 fails to teach or suggest the use of an IRES sequence in the vectors described therein which encode UTV sequences. Therefore, U.S. Patent No. 6,465,253 fails to teach or suggest each and every limitation of claims 13, 21, 25, and 28.

U.S. Patent No. 6,465,253 also fails to teach each and every limitation of claim 38 as it does not teach or suggest an expression vector comprising an HBEGF gene which is ***fused*** to a second selection gene or a vector comprising a site which allows for ***functional separation*** of the two genes.

With respect to publication No. US 2002/0168649 (U.S. Patent Application Serial No. 09/966,976) Applicants submit that US 2002/0168649 and the instant application were, at the time the invention of US 2002/0168649 was made, both owned by Rigel Pharmaceuticals, Inc. Therefore, under 35 U.S.C. §103(c), publication No. US 2002/0168649 is disqualified from being used in a rejection under 35 U.S.C. §103(a) against the claims of the instant application. As set forth above, the remaining reference, U.S. Patent No. 6,465,253, fails to teach or suggest each and every limitation of the claims. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

CONCLUSION

In view of the amendments set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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